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Original Article

Effect of a leukotriene receptor antagonist on the prevention of recurrent asthma attacks after an emergency room visit

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Abstract

Background: The efficacy of montelukast, a specific cysteinyl leukotriene receptor antagonist, in preventing recurrent asthma attacks was evaluated for post-emergency management of acute asthma exacerbation.

Methods: Twenty-two patients with a history of chronic asthma whose symptoms were responsive to an inhaled β-adrenergic receptor agonist in an emergency room setting, were randomized into two groups, those with and those without montelukast ($n = 11$ for each group). Patients in the montelukast group received an oral dose of 10 mg montelukast before leaving the emergency room following rescue treatment with an inhaled β-adrenergic receptor agonist. Patients in both groups were instructed to use an inhaled β-adrenergic receptor agonist for shortness of breath or dyspnea in post-emergency management. Additional β-adrenergic receptor agonist use, subjective asthma symptoms, sleep impairment, additional emergency visits and/or hospitalization were monitored for 24 hours following the emergency room visit.

Results: In the montelukast group, the need for a rescue β-adrenergic receptor agonist was significantly decreased; 54.5% of patients in the montelukast group required use of β-adrenergic receptor agonist compared with 100% in the non-montelukast group ($P < 0.05$). The average number of uses of a β-adrenergic receptor agonist was 2.67 ± 3.58 times/24 h in the montelukast group compared with 11.95 ± 3.60 times/24 h in the non-montelukast group ($P < 0.01$). The average subjective asthma symptom scores were significantly decreased in the montelukast group, whereas no score change occurred in the non-montelukast group. The sleep impairment score was significantly lower in the montelukast group compared with that in the non-montelukast group ($P < 0.05$). No patients in either group had an emergency visit or hospitalization during this period.

Conclusions: The results demonstrate that montelukast can prevent recurrent asthma exacerbations in the home environment.

Key words: β_2-adrenergic receptor agonist, asthma exacerbation, leukotriene receptor antagonist, montelukast.

Introduction

In the management of asthma, the choice of drugs for controlling recurrent acute asthma exacerbations, especially in the home environment, is important for patients who have been released from hospital emergency care. Continuous use of inhaled β-adrenergic receptor agonists in combination with systemic administration of corticosteroids was recommended by the Global Initiative for Asthma (GINA) guidelines (2002) as a treatment for such conditions.[1] However, systemic corticosteroids

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are slow acting and it takes 4–6 h for the clinical effects of systemic corticosteroids to be manifested on acute asthma exacerbation.[2] In contrast, β-adrenergic receptor agonists are rapid and short acting, but they are effective only in a portion of acute asthmatic patients.[3] Thus, no adequate progress has been made in the drug treatment of acute asthma over the past 20 years,[4] despite the fact that the prevalence of emergency room visits following an acute asthma attack has increased substantially.

Leukotriene (LT) receptor antagonists have emerged as an important treatment for the long-term control of chronic asthma.[5,6] Evidence suggesting the clinical benefit of LT receptor antagonists has accumulated in acute asthmatic patients and their effectiveness is due to the rapid onset of their bronchodialating effect.[7,8] In the present study, we examine the effect of montelukast, a LT receptor antagonist, in the prevention of the recurrence of acute asthma exacerbations in patients who have been released after receiving rescue β-adrenergic receptor agonist treatment in an emergency room.

METHODS

The subjects of the present study were 22 patients with a 1 year or more history of asthma, whose mild to moderate asthma exacerbations responded to the use of inhaled β-adrenergic agonists in an emergency care visit. None of the study subjects had received systemic corticosteroid therapy. An improvement of acute asthma exacerbation with β-adrenergic receptor agonists was measured in terms of physical parameters, such as auscultatory findings, heart rate and respiratory rate, and symptoms of respiratory distress lasting for 1 h or more in an emergency room visit.

Subjects were randomized into two groups: those patient given montelukast and those not ($n = 11$ for each group). While still in the emergency room, patients in the montelukast group received a single oral dose of 10 mg montelukast just after rescue treatment with an inhaled β-adrenergic receptor agonist and were prescribed montelukast for 3 days. Patients in the non-montelukast group received no medication other than the initial rescue treatment. The study subjects excluded patients who needed further intensive treatment, such as in-patient care, those who had previously used LT receptor antagonists and those who had been using nebulized β-adrenergic receptor agonists in the home environment.

As post-emergency room management, both groups were instructed to use inhaled β-adrenergic receptor agonists with a metered-dose inhaler for recurrent asthma exacerbations as needed and to take a second dose of the β-adrenergic receptor agonist if the recurrent attack was not relieved within 30 min of the first dose. If the attack persisted after the second dose, patients were instructed to return to the emergency room.

The primary end-point for evaluating recurrence of asthma exacerbation in the home environment was the frequency of inhaled β-adrenergic receptor agonist use, which was monitored in the 24 h period between release from the emergency care visit and the out-patient visit of the following day, and was expressed as the calculated number of β-adrenergic receptor agonist uses per 24 h. The secondary end-points were subjective asthma symptom scores, nocturnal sleep impairment scores and number of emergency visits or hospitalizations. The scores of subjective asthma symptoms and nocturnal sleep impairment for the worst asthmatic attack before and after the emergency visit were determined according to the criteria of the Japanese Society of Allergology (Table 1) in patient interviews.[9]

Data are expressed as the mean ± SD. Differences between groups were analyzed by Student's *t*-tests and Fisher's exact test at a two-tailed significance of 5%.

RESULTS

Baseline patient characteristics of both groups are shown in Table 2. The treatment programs for asthma before the emergency care visit were similar in the two groups. Home management of chronic asthma in all patients was not adequately sustained, even with clinic visits. Both the average severity of asthma in the home environment measured with subjective asthma symptom scores prior to the emergency visit and mean room air S_pO_2 at the emergency visit were similar in both groups.

Frequency of inhaled β-adrenergic receptor agonist use

Subsequent to the emergency visit, all te patients in the non-montelukast group needed inhaled β-adrenergic receptor agonists, whereas only six patients (54.5%) in the montelukast group did ($P < 0.05$). The frequency of β-adrenergic receptor agonist use was significantly lower in the montelukast group compared with the non-montelukast group (2.67 ± 3.58 and 11.95 ± 3.60 times/24 h, respectively; $P < 0.01$; Fig. 1).

Table 1 Criteria of asthma symptoms and nocturnal sleep impairment scores prepared by the Japanese Society of Allergology[9]

	Score (points)
Asthma symptom scores	
Severe asthma exacerbation	9
Moderate asthma exacerbation	6
Mild asthma exacerbation	3
Wheeze	1
Severe cough	0.5
Mild cough	0.5
None	0
Nocturnal sleep impairment scores	
Not possible because of respiratory distress	9
Difficult because of respiratory distress	6
Fairly possible despite respiratory distress	3
Peaceful	0

Table 2 Characteristics of study subjects

Characteristics	Non-montelukast group ($n = 11$)	Montelukast group ($n = 11$)
Mean (± SD) ages (years)	41.2 ± 15.5	40.9 ± 16.9
Sex (no. males/females)	5/6	4/7
Mean (±SD) duration of asthma (years)	12.6 ± 15.3	9.8 ± 10.9
Smoking (no. smokers/non-smokers)	4/7	4/7
Severity (no. mild/moderate/severe)	7/4/0	6/5/0
Mean (± SD) attack score before emergency visit (points)	3.1 ± 1.2	3.1 ± 1.7
Treatment programs for asthma before the emergency visit (*n*)		
No regular treatment program	5	5
Oral β-adrenergic receptor agonists as needed	1	1
Inhaled β-adrenergic receptor agonists as needed	4	3
Irregular inhaled corticosteroids	1	2

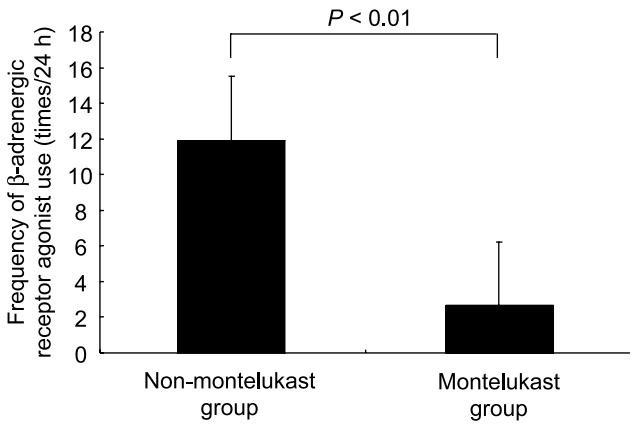

Fig. 1 Frequency of inhaled β-adrenergic receptor agonist use, monitored in the 24 h period between the release from emergency care visit and the out-patient visit of the following day, expressed as the calculated number of β-adrenergic receptor agonist uses per 24 h. Values are the mean ± SD for $n = 11$ subjects per group.

Subjective asthma symptom score

Changes in the average subjective asthma symptom score at the worst asthma attack before and after the emergency care visit were from 3.05 ± 1.23 to 2.64 ± 1.55 in the group without montelukast and from 3.14 ± 1.67 to 0.82 ± 0.78 in the montelukast group (Fig. 2). The decrease was significant in the montelukast group ($P < 0.01$), but not in the non-montelukast group ($P = 0.51$).

When the percentage change from baseline in the score of individual patients was calculated and then averaged, the average percentage reduction from baseline was significantly higher in the montelukast group than in the non-montelukast group (59.8 ± 39.6 and 6.1 ± 48.5%, respectively; $P < 0.05$).

Nocturnal sleep impairment score

The nocturnal sleep impairment score after an emergency care visit was significantly lower (2.72 ± 2.10) in the montelukast group compared with the non-montelukast group (5.45 ± 1.23), suggesting that nocturnal sleep was significantly improved with montelukast ($P < 0.01$; Fig. 3).

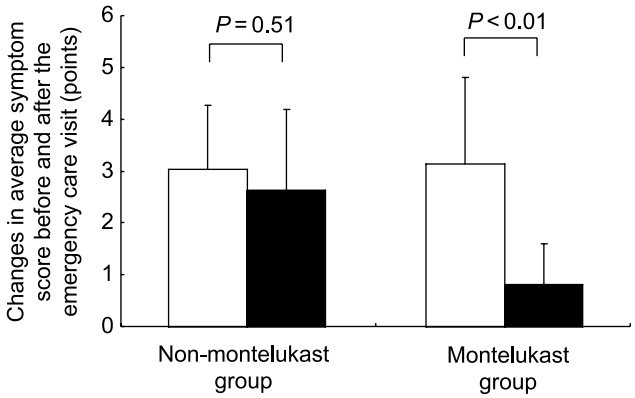

Fig. 2 Changes in the average subjective asthma symptom score at the worst asthma attack before (□) and after (■) the emergency care visit. The scores of subjective asthma symptoms were taken according to the criteria of the Japanese Society of Allergology[9] in patient interviews. Values are the mean ± SD for $n = 11$ subjects per group.

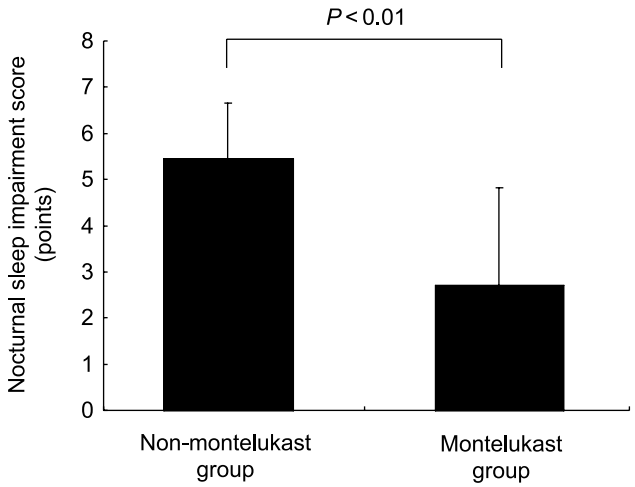

Fig. 3 Nocturnal sleep impairment scores after an emergency care visit. The scores of nocturnal sleep impairment were taken according to the criteria of the Japanese Society of Allergology[9] in patient interviews. Values are the mean ± SD for $n = 11$ subjects per group.

Number of emergency return visits and/or hospitalizations

No patient in either group returned to the emergency room or was hospitalized subsequent to the emergency care visit.

Discussion

In the present clinical study in emergency room asthmatic patients whose acute exacerbation responded to rescue β-adrenergic receptor agonists, a single oral dose of montelukast given before leaving the emergency room significantly reduced the subsequent use of β-adrenergic receptor agonists, as well as scores of subjective asthma symptoms and sleep disturbance. The results demonstrate the beneficial effect of montelukast in the home management of recurrent asthma exacerbations.

The pathophysiology of asthma has become increasingly more understood in recent years. The drugs of first choice for the treatment of an asthma attack in the emergency room have been short-acting β-adrenergic receptor agonists, according to the treatment guidelines for acute asthma.[1] When patients are relieved from an acute asthma attack by treatment, and the ameliorating effect continues, they are allowed to go home after an adequate home management program for recurrent attacks is given. In the GINA guidelines, the continual use of inhaled β-adrenergic receptor agonists in combination with systemic corticosteroids has been recommended for such post-emergency management of asthma exacerbations.[1] However, this treatment is inadequate as the management method for the following reasons: (i) approximately one-third of patients in an emergency setting poorly respond to short-acting β-adrenergic receptor agonists;[3] and (ii) corticosteroids have a delayed clinical effect, resulting in 4–6 h or even longer before patients have relief.[2] Furthermore, the use of systemic corticosteroids in patients with acute asthma does not improve pulmonary function within 6 h of their administration nor do systemic corticosteroids reduce hospitalizations of such patients, as revealed in a recent meta-analysis.[10] Although the alternative combination of an inhaled anticholinergic agent and an inhaled β-adrenergic receptor agonist produced a better bronchodilating effect and reduced the number of hospitalizations in patients with acute asthma,[11] anticholinergic agents themselves have been ineffective in the treatment of

β-adrenergic receptor agonist-resistant asthma exacerbations and, in the study of McFadden *et al.*, the presence of an anticholinergic agent in the β-adrenergic receptor agonist regimen did not influence the treatment effect.[12] The effects of intravenous injections of methylxanthine,[13] magnesium[14] and helium–oxygen therapy[15] have been investigated for the same clinical aspect, but there has been no conclusive consensus reached yet regarding their beneficial effects in the treatment of acute asthma. Thus, finding a drug that has fast action and a sustained effect for preventing recurrent asthma exacerbations is one of the important goals in the post-emergency management of acute asthma.

Cysteinyl LT are implicated in acute asthma, as evidenced by the elevated cysteinyl LT concentration in urine and induced sputum during an acute asthma attack.[16,17] The metabolites of arachidonic acid, produced by 5-lipoxygenase, mediate not only inflammatory cell chemotaxis of eosinophils and microvascular permeability, but also bronchial smooth muscle constriction and proliferation.[18,19]

Leukotriene receptor antagonists are considered effective drugs for the long-term control of chronic asthma according to the GINA guidelines.[1] Dockhorn *et al*. demonstrated that both oral and intravenous montelukast improved respiratory function in patients with chronic asthma.[20] The improvement in forced expiratory volume in 1 s (FEV_1) is much greater at 15 min after intravenous administration and the effect continued for 24 h with a single oral or intravenous dose of montelukast, suggesting the relatively fast and sustained bronchodilating effect of LT receptor antagonists. The effect of an LT receptor antagonist in the prevention of acute asthma was also indicated in a study in which administration of the drug significantly inhibited airway constriction in response to exercise,[21] the inhalation of cold air[22] or allergens[23] in patients with bronchial asthma. Clinical data for the use of LT receptor antagonists in acute asthmatic patients continue to accumulate. Camargo *et al*. compared the effect of standard therapy (placebo group) with that of a combination of standard therapy and intravenous montelukast (montelukast group) in patients with acute asthma who did not respond to an inhaled β-adrenergic receptor agonist.[7] Montelukast improved FEV_1 over 20 min after administration. The mean FEV_1 increased significantly from prerandomization baseline and the use of systemic corticosteroids or β-adrenergic receptor agonists was significantly less in patients in the montelukast group compared with the placebo group. In a study of acute asthmatic patients, peak respiratory flow increased more in the group treated with a combination of the systemic corticosteroid and oral montelukast compared with systemic corticosteroid alone, although the difference between the two groups was not significant.[8] Leukotriene receptor antagonists may be more effective in the management of acute asthma rather than in the long-term control of chronic asthma because the cysteinyl LT production pathway is more active in acute asthma than in the chronic form of the condition.[16,17] However, there is not enough evidence that LT receptor antagonists are more effective as relievers of acute asthma than as controllers of chronic asthma; thus, further investigation of the significance of inhibiting cysteinyl LT activity during asthma exacerbations is needed.

Although none of the subjects in the present study sustained home management of chronic asthma adequately, all subjects were responded to an inhaled β-adrenergic receptor agonist in emergency care. However, the effect of the β-adrenergic receptor agonist was transient, as evidenced by the need for additional doses of the inhaled β-adrenergic receptor agonist for recurrent exacerbation in both groups. Montelukast reduced the use of the β-arenergic receptor agonist, subjective asthma symptom scores and nocturnal sleep impairment scores, suggesting the effectiveness of LT receptor antagonists in the prevention of recurrent asthma attacks in patients with β-adrenergic receptor agonist-responsive acute asthma whose chronic asthma management is not adequately sustained. In fact, approximately half the patients in the montelukast group needed to use a β-adrenergic receptor agonist to some extent, but only one of them needed to use it as often as the patients in the non-montelukast group. In many previous studies, LT receptor antagonists have been shown to possess several anti-asthmatic effects, such as broncodilation and anti-inflammatory effects. The rapid onset of action obtained in the present clinical study suggests that the primary mechanism of action of LT receptor antagonists in the management of acute asthma is one of bronchodilation. Although the impact of LT receptor antagonists on respiratory function with time during asthma exacerbations was not investigated in the present study, this information is needed to clarify the precise mechanism of action of LT receptor antagonists.

There was a population of asthmatic patients who were responsive to LT receptor antagonists and one that was not: responders and non-responders found in the study of the long-term control of chronic asthma.[24–26]

Involvement of variants of the LTC_4 synthase gene and the 5-lipoxygenase gene in responsiveness to LT receptor antagonists has been suggested in some studies.[24–26] However, Camargo *et al*. reported that the bronchodialating effect of montelukast on acute asthma was observed in the majority of patients and their results did not confirm the obvious existence of responders or non-responders.[7]

The results of the present study demonstrate the beneficial effect of montelukast in the management of mild asthma exacerbations without the need for the administration of systemic corticosteroids. However, further investigation is needed to elucidate the role and importance of cysteinyl LT in the inflammation and constriction of the pulmonary pathway in acute asthma and the significance of inhibiting cysteinyl LT activity in acute asthma. Large-scale studies are needed to evaluate the therapeutic efficacy and usefulness of LT receptor antagonists in patients with acute asthma, including comparisons with anticholinergic agents and long-acting β-adrenergic receptor agonists. In addition, the aim of the present clinical study was not to compare the effectiveness directly between established systemic corticosteroids therapy and LT receptor antagonists in the management of asthma exacerbations. Either a comparative study with systemic corticosteroid therapy or an investigation of the add-on effect of LT receptor antagonists to systemic corticosteroid therapy is needed to prove the clinical usefulness of LT receptor antagonists in the management of acute asthma.

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